Agency for Healthcare Research and Quality
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NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

ACG clinical guidelines: diagnosis and management of celiac disease.

Bibliographic Source(s)

Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol. 2013 May;108(5):656-76. [264 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The definitions for quality of evidence (high, moderate, and low) and strength of recommendations (strong or conditional) are provided at the end of the "Major Recommendations" field.

When to Test for Celiac Disease (CD)

1. Patients with symptoms, signs, or laboratory evidence suggestive of malabsorption, such as chronic diarrhea with weight loss, steatorrhea, postprandial abdominal pain, and bloating, should be tested for CD (Strong recommendation, high level of evidence).
2. Patients with symptoms, signs, or laboratory evidence for which CD is a treatable cause should be considered for testing for CD (Strong recommendation, moderate level of evidence).
3. Patients with a first-degree family member who has a confirmed diagnosis of CD should be tested if they show possible signs or symptoms or laboratory evidence of CD (Strong recommendation, high level of evidence).
4. Consider testing of asymptomatic relatives with a first-degree family member who has a confirmed diagnosis of CD (Conditional recommendation, high level of evidence).
5. CD should be sought among the explanations for elevated serum aminotransferase levels when no other etiology is found (Strong recommendation, high level of evidence).
6. Patients with Type I diabetes mellitus (DM) should be tested for CD if there are any digestive symptoms, or signs, or laboratory evidence suggestive of CD (Strong recommendation, high level of evidence).

Diagnosis of CD

1. Immunoglobulin A (IgA) anti-tissue transglutaminase (TTG) antibody is the preferred single test for detection of CD in individuals over the

age of 2 years (Strong recommendation, high level of evidence).
2. When there exists a high probability of CD wherein the possibility of IgA deficiency is considered, total IgA should be measured. An alternative approach is to include both IgA and immunoglobulin G (IgG) based testing, such as IgG-deamidated gliadin peptides (DGPs), in these high-probability patients (Strong recommendation, moderate level of evidence).
3. In patients in whom low IgA or selective IgA deficiency is identified, IgG-based testing (IgG DGPs and IgG TTG) should be performed (Strong recommendation, moderate level of evidence).
4. If the suspicion of CD is high, intestinal biopsy should be pursued even if serologies are negative (Strong recommendation, moderate level of evidence).
5. All diagnostic serologic testing should be done with patients on a gluten-containing diet (Strong recommendation, high level of evidence).
6. Antibodies directed against native gliadin are not recommended for the primary detection of CD. (Strong recommendation, high level of evidence).
7. Combining several tests for CD in lieu of TTG IgA alone may marginally increase the sensitivity for CD but reduces specificity and therefore are not recommended in low-risk populations (Conditional recommendation, moderate level of evidence).
8. When screening children younger than 2 years of age for CD, the IgA TTG test should be combined with DGP (IgA and IgG) (Strong recommendation, moderate level of evidence).

Confirmatory Testing in CD

1. The confirmation of a diagnosis of CD should be based on a combination of findings from the medical history, physical examination, serology, and upper endoscopy with histological analysis of multiple biopsies of the duodenum (Strong recommendation, high level of evidence).
2. Upper endoscopy with small-bowel biopsy is a critical component of the diagnostic evaluation for persons with suspected CD and is recommended to confirm the diagnosis (Strong recommendation, high level of evidence).
3. Multiple biopsies of the duodenum (one or two biopsies of the bulb and at least four biopsies of the distal duodenum) are recommended to confirm the diagnosis of CD (Strong recommendation, high level of evidence).
4. Lymphocytic infiltration of the intestinal epithelium in the absence of villous atrophy is not specific for CD and other causes should also be considered (Strong recommendation, high level of evidence).

Role of Ancillary Testing in CD

1. HLA-DQ2/DQ8 testing should not be used routinely in the initial diagnosis of CD (Strong recommendation, moderate level of evidence).
2. HLA-DQ2/DQ8 genotyping testing should be used to effectively rule out the disease in selected clinical situations (Strong recommendation, moderate level of evidence).
3. Examples of such clinical situations include but are not limited to:
    a. Equivocal small-bowel histological finding (Marsh I-II) in seronegative patients
    b. Evaluation of patients on a gluten-free diet (GFD) in whom no testing for CD was done before GFD
    c. Patients with discrepant celiac-specific serology and histology
    d. Patients with suspicion of refractory CD where the original diagnosis of celiac remains in question
    e. Patients with Down's syndrome
4. Capsule endoscopy should not be used for initial diagnosis except for patients with positive-celiac specific serology who are unwilling or unable to undergo upper endoscopy with biopsy (Strong recommendation, moderate level of evidence).
5. Capsule endoscopy should be considered for the evaluation of small-bowel mucosa in patients with complicated CD (Strong recommendation, moderate level of evidence).
6. Intestinal permeability tests, D-xylose, and small-bowel follow-through are neither specific nor sensitive and are not recommended for CD diagnosis (Strong recommendation, moderate level of evidence).
7. Stool studies or salivary tests are neither validated nor recommended for use in the diagnosis of CD (Strong recommendation, weak level of evidence).

Differentiation of CD from Non-Celiac Gluten Sensitivity

1. Symptoms or symptom response to a GFD alone should not be used to diagnose CD, as these do not differentiate CD from non-celiac gluten sensitivity (Strong recommendation, moderate level of evidence).
2. A diagnosis of non-celiac gluten sensitivity should be considered only after CD has been excluded with appropriate testing (Strong recommendation, moderate level of evidence).

Diagnosis Among Patients on a GFD

1. While standard diagnostic tests (specific serology and intestinal biopsy) have a high positive predictive value (PPV) for CD, they should not be relied upon to exclude CD in patients already adhering to a GFD (Strong recommendation, high level of evidence).
2. HLA-DQ2/DQ8 genotyping should be used to try to exclude CD prior to embarking on a formal gluten challenge (Strong recommendation, high level of evidence).
3. CD should be differentiated from non-celiac gluten sensitivity in order to identify the risk for nutritional deficiency states, complications of CD, risk for CD and associated disorders in family members, and to influence the degree and duration of adherence to the GFD (Conditional recommendation, moderate level of evidence).
4. Formal gluten challenge should be considered, where necessary, to diagnose or exclude CD in patients already adhering to a GFD (Strong recommendation, high level of evidence).
5. Despite the disadvantages of neither confirming nor excluding a diagnosis of CD, some patients will opt to continue on a strictly GFD without undergoing formal gluten challenge; such patients should be managed in a similar fashion to those with known CD (Conditional recommendation, low level of evidence).

Management of CD

1. People with CD should adhere to a GFD for life. A GFD entails strict avoidance of all products containing the proteins from wheat, barley, and rye (Strong recommendation, high level of evidence).
2. While pure oats appear to be safely tolerated by the majority of people with CD, oats should be introduced into the diet with caution and patients should be monitored closely for evidence of adverse reaction (Strong recommendation, moderate level of evidence).
3. People with CD should be referred to a registered dietitian who is knowledgeable about CD in order to receive a thorough nutritional assessment and education on the GFD (Strong recommendation, moderate level of evidence)
4. People with newly diagnosed CD should undergo testing and treatment for micronutrient deficiencies. Deficiencies to be considered for testing should include, but not be limited to, iron, folic acid, vitamin D, and vitamin B12 (Conditional recommendation, low level of evidence).

Monitoring of CD

1. People with CD should be monitored regularly for residual or new symptoms, adherence to GFD, and assessment for complications. In children, special attention to assure normal growth and development is recommended (Strong recommendation, moderate level of evidence).
2. Periodic medical follow-up should be performed by a health-care practitioner with knowledge of CD. Consultation with a dietitian should be offered if gluten contamination is suspected (Strong recommendation, moderate level of evidence).
3. Monitoring of adherence to GFD should be based on a combination of history and serology (IgA TTG or IgA [or IgG] DGP antibodies) (Strong recommendation, moderate level of evidence).
4. Upper endoscopy with intestinal biopsies is recommended for monitoring in cases with lack of clinical response or relapse of symptoms despite a GFD (Strong recommendation, moderate level of evidence).
5. Monitoring of people with CD should include verification of normalization of laboratory abnormalities detected during initial laboratory investigation (Strong recommendation, moderate level of evidence).

Non-Responsive CD (NRCD) or Refractory CD (RCD)

1. Patients with NRCD should be evaluated carefully to identify and treat the specific etiology in each patient (Strong recommendation, high level of evidence).
2. Early steps in the evaluation should include measurement of celiac serologies and a thorough review of the patient's diet by a dietitian who is experienced in CD management (Strong recommendation, high level of evidence).
3. Differentiation should be made between Type I and Type II refractory CD as this is important for management and prognosis (Strong recommendation, moderate level of evidence).
4. Treatment with medication, as an adjunct to the GFD, should be considered in refractory CD (Conditional recommendation, moderate level of evidence).
5. Patients with RCD should be monitored closely and receive aggressive nutritional support including parenteral nutrition whenever indicated (Strong recommendation, high level of evidence).

Definitions:

Definition of Grades of Evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to grade the quality of evidence.

High = Further research is unlikely to change our confidence in the estimate of effect

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very Low = Any estimate of effect is very uncertain

Strength of Recommendations

A "strong" recommendation is made when the benefits clearly outweigh the negatives and the result of no action. "Conditional" is used when some uncertainty remains about the balance of benefit/potential harm.

Clinical Algorithm(s)

The original guideline document contains clinical algorithms for:

- Celiac disease (CD) diagnostic testing
- An approach to gluten challenge for the diagnosis or exclusion of CD in patients maintained on a gluten-free diet without prior definitive diagnostic testing
- An approach to monitoring CD
- An approach to the investigation of non-responsive celiac disease (NRCD) and refractory celiac disease (RCD)

Scope

Disease/Condition(s)

Celiac disease (CD)

Guideline Category

Diagnosis

Evaluation

Management

Prevention

Risk Assessment

Screening

Treatment

Clinical Specialty

Family Practice

Gastroenterology

Internal Medicine

Intended Users

Physicians

Guideline Objective(s)

To provide recommendations for the diagnosis, treatment, and overall management of patients with celiac disease (CD), including an approach to the evaluation of non-responsive CD

Target Population

Patients with celiac disease

Note: While the original guideline document is primarily directed at the care of adult patients, variations pertinent to the pediatric population have been included.

Interventions and Practices Considered

Diagnosis/Assessment

1. Medical history and physical examination
2. Patients with symptoms, signs, or laboratory evidence of celiac disease (CD), especially if there is a first-degree family member who has a confirmed diagnosis of CD, should be considered for testing for CD
3. Serologic testing (while on a gluten-containing diet)
4. Immunoglobulin A (IgA) anti-tissue transglutaminase (TTG) antibody testing
5. Immunoglobulin G (IgG)-deamidated gliadin peptides (DGPs)
6. Endoscopy
7. Intestinal biopsy with histological analysis
8. Screening children younger than 2 years of age
9. HLA-DQ2/DQ8 genotyping testing
10. Capsule endoscopy
11. Formal gluten challenge
12. Risk assessment for nutritional deficiency states, complications of CD, risk for CD and associated disorders in family members
13. Testing for micronutrient deficiencies

Management/Treatment

1. Gluten free diet (GFD)
2. Referral to a registered dietitian
3. Treatment for micronutrient deficiencies (including, but not be limited to, iron, folic acid, vitamin D, and vitamin B12)
4. Monitoring and assessment for complications of CD (special attention to normal growth and development in children)
5. Medical follow-up
6. Monitoring of adherence to GFD should be based on a combination of history and serology (IgA TTG or IgA [or IgG] DGP antibodies)
7. Upper endoscopy with intestinal biopsies is recommended for monitoring (as indicated)
8. Management of patients with non-responsive CD (NRCD) or refractory CD (RCD)
    - Measurement of celiac serologies
    - Review of the patient's diet
    - Differentiation between Type I and Type II RCD
    - Medication (as adjunct to GFD)
    - Close monitoring and receive aggressive nutritional support (parenteral nutrition when indicated)

Major Outcomes Considered

- Predictive/ prognostic value of risk assessment and diagnostic tests
- Efficacy of treatment

- Symptom control
- Adherence to treatment regimen
- Clinical outcomes
- Incidence of refractory symptoms
- Quality of life

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A search of PubMed, MEDLINE and the Cochrane database was performed using the search terms 'celiac disease', 'celiac sprue', 'gluten sensitive enteropathy', 'diagnosis' and 'treatment' for years 1980–2011. The search was limited to English language and humans. Systematic reviews and meta-analyses were used as primary sources when available.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Definition of Grades of Evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to grade the quality of evidence.

High = Further research is unlikely to change our confidence in the estimate of effect

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very Low = Any estimate of effect is very uncertain

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

See the "Rating Scheme for the Strength of the Evidence" field.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

See the "Rating Scheme for the Strength of the Recommendations" field.

Rating Scheme for the Strength of the Recommendations

A "strong" recommendation is made when the benefits clearly outweigh the negatives and the result of no action. "Conditional" is used when some uncertainty remains about the balance of benefit/ potential harm.

Cost Analysis

A cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

In an effort to make our new guidelines as "fresh" as possible when published, we have created a special guideline review process, involving members of the Board of Trustees, Practice Parameters Committee and the American Journal of Gastroenterology. It is our goal to review the guideline, allow you to revise the guideline, and re-review the guideline within 6 months of first submission. Therefore the entire process should take 1 year from commission to finished, accepted guideline.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis and management of patients with celiac disease (CD)

Potential Harms

While pure oats appear to be safely tolerated by the majority of people with celiac disease (CD), oats should be introduced into the diet with caution and patients should be monitored closely for evidence of adverse reaction.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 May

Guideline Developer(s)

American College of Gastroenterology - Medical Specialty Society

Source(s) of Funding

The authors are supported by National Institutes of Health (NIH) DK-57982 (J.A.M.), 1K08 DK090150 (A.H.C.), and American College of Gastroenterology Junior Faculty Development Award (A.R.-T.).

Guideline Committee

American College of Gastroenterology Practice Parameters Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Potential Competing Interests

Dr. Rubio-Tapia and Dr. Calderwood have nothing to declare. Dr. Hill serves on the editorial boards of the Journal of Pediatrics and Journal of Pediatric Gastroenterology and Nutrition. Dr. Kelly acts or has acted as a scientific and medical advisor to Alba, Alvine, and ImmunosanT and has received research funding support on celiac disease (CD) from Alba and Shire. Dr. Murray has received grant support from Alba Therapeutics (>$50,000), served on the Advisory Board of Alvine Pharmaceuticals (<$10,000), and served as consultant to Ironwood (<$10,000), Flamentera (<$10,000), Actogenix (<$10,000), Bayer Healthcare Pharmaceuticals (<$10,000), Vysera Biomedical (<$10,000), 2G Pharma (<$10,000), ImmunosanT (<$10,000), and Shire US (<$10,000).

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the American College of Gastroenterology (ACG) Web site.

Availability of Companion Documents

The following is available:

- American College of Gastroenterology Practice Parameters Committee. Guideline development policies. 2010 Jan. Available from the American College of Gastroenterology (ACG) Web site.

Patient Resources

Information on celiac disease is available on the American College of Gastroenterology's Patient Education & Resource Center Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on June 19, 2013. The information was verified by the guideline developer on July 30, 2013.

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